



King's Research Portal

DOI:

[10.1016/j.jad.2017.08.041](https://doi.org/10.1016/j.jad.2017.08.041)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Leppanen, J., Wee Ng, K., Kim, Y-R., Tchanturia, K., & Treasure, J. (2018). Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans. *Journal of Affective Disorders*, 225, 167-179. <https://doi.org/10.1016/j.jad.2017.08.041>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

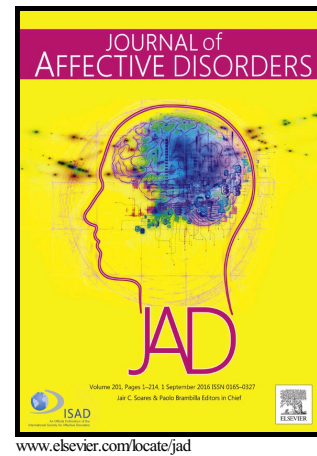
Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Author's Accepted Manuscript

Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans

Jenni Leppanen, Kah Wee Ng, Youl-Ri Kim, Kate Tchanturia, Janet Treasure



PII: S0165-0327(17)30930-8
DOI: <http://dx.doi.org/10.1016/j.jad.2017.08.041>
Reference: JAD9160

To appear in: *Journal of Affective Disorders*

Received date: 9 May 2017
Revised date: 23 June 2017
Accepted date: 14 August 2017

Cite this article as: Jenni Leppanen, Kah Wee Ng, Youl-Ri Kim, Kate Tchanturia and Janet Treasure, Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans, *Journal of Affective Disorders*, <http://dx.doi.org/10.1016/j.jad.2017.08.041>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans

Ms. Jenni Leppanen^{1*}, Dr. Kah Wee Ng², Dr. Youl-Ri Kim³, Dr. Kate Tchanturia^{1,4}, Prof. Janet Treasure¹

¹ King's College London, Institute of Psychiatry, Psychology, and Neuroscience, Department of Psychological Medicine, London, United Kingdom

² Singapore General Hospital, 20 College Road, Academia, Singapore, 169865

³ Department of Psychiatry, Seoul Paik Hospital, Inje University, Seoul, South Korea

⁴ Department of Psychology, Ilia State University, Tbilisi, Georgia

* Corresponding author:

Jenni Leppanen, Department of Psychological Medicine, Institute of Psychiatry, Psychology, & Neuroscience, King's College London, 103 Denmark Hill, London, SE5 8AF, UK. Email: jenni.leppanen@kcl.ac.uk

Keywords: oxytocin, threat processing, startle, attention, approach, avoidance

1 Abstract

Background: Heightened threat sensitivity is a transdiagnostic feature in several psychiatric disorders. The neuropeptide oxytocin has been shown to reduce fear related behaviours and facilitated fear extinction in animals. These findings have led to increasing interest to explore the effects of intranasal oxytocin on threat processing in humans.

Methods: The review included 26 studies (N = 1173), nine of which included clinical populations (N = 234). The clinical groups included were people with borderline personality disorder (BPD), anorexia nervosa, bulimia nervosa, depression, anxiety, and alcohol dependence disorder. We examined the effects of a single dose of intranasal oxytocin on startle response, attentional responses, and behavioural responses to threat.

Results: A single dose of intranasal oxytocin significantly increased the physiological startle response to threat in healthy people with a small effect size. However, oxytocin did not have significant effects on attentional bias towards social or disorder-specific threat, fixation towards threatening stimuli among healthy or clinical populations, or on threat related behavioural approach or avoidance responses.

Limitations: No studies investigated the effects of oxytocin on the startle response to threat among clinical populations. Additionally, only one of the reviewed studies had sufficient power to detect at least a moderate effect of oxytocin according to our criterion.

Discussion: The synthesis of literature suggest that oxytocin may influence the salience of threatening stimuli among healthy individuals, increasing the startle response to threat. It would be of interest to investigate the effects of oxytocin on the startle response to threat among clinical populations.

2 Introduction

Threat processing is vital for the survival of an organism or species (Öhman, 2005; Öhman, 2007). Potential threats are rapidly recognised and activate a number of subcortical structures including the amygdala and the hypothalamic-pituitary-adrenal (HPA) axis, which initiate protective fear responses (Öhman 2005). Physiological responses, such as increased skin conductance, behavioural approach and avoidance responses, such as fight or flight responses, and attentional responses, such as active attending to the source of fear also occur (Misslin 2003). However, hypersensitivity of this system and maladaptive fear learning can have negative consequences (Ozawa and Johansen, 2014). Such maladaptive processes are believed to contribute to the development and maintenance of number of psychiatric disorders, such as eating disorders (ED), anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) (Britton et al., 2011; Ozawa and Johansen, 2014; Strober et al., 2007).

Behavioural studies have demonstrated that people with PTSD, OCD, and ED show anomalies in physiological response to threat. For example, there is an exaggerated physiological startle response to anticipation and viewing of disorder-specific, potentially threatening stimuli, such as images of trauma, contamination, or food (Altman et al., 2013; Mauler et al., 2006; Pitman et al., 2012; Simon et al., 2013). Additionally, a number of reviews have reported atypical attentional bias towards disorder specific stimuli (Bar-Haim et al., 2007; Brooks et al., 2011; Cisler and Koster, 2010). Furthermore, disorder specific stimuli have been found to elicit negative facial expressions and subjective feelings of fear and disgust (Broderick et al., 2013; Soussignan et al., 2011; Uher et al., 2004). Taken together these findings suggest that treatments targeting this hypersensitivity and maladaptive fear learning may be of benefit.

The neuropeptide, oxytocin, has been found to play an important regulatory role in human and animal studies (Neumann and Slattery, 2016; Onaka et al., 2012; Zheng et al., 2010). Animal studies

have demonstrated that oxytocin plays an important role in lowering the physiological stress and anxiety response by activating a negative feedback loop (Onaka et al., 2012; Zheng et al., 2010). Elevated oxytocin secretion from the paraventricular nucleus of the hypothalamus following a stressful event is believed to lead to increased availability of gamma-aminobutyric acid (GABA), which in turn is believed to inhibit the HPA axis and amygdala activation (Onaka et al., 2012; Zheng et al., 2010). Indeed, a recent study found that marmoset monkeys treated with an oxytocin receptor antagonist had elevated glucocorticoid levels in response to the stressor and showed a greater tendency to engage in maladaptive fear-related behaviour such as isolation (Cavanaugh et al., 2016). These findings have sparked increasing interest in exploring the role of oxytocin in threat processing, particularly in fear responses and extinction learning.

Preclinical studies demonstrated that exogenous intravenous and intranasal oxytocin can influence fear related responses in rodents and monkeys respectively, reducing hiding behaviour during an open field test and attentional bias towards threatening facial expressions (Parr et al., 2013; Rotzinger et al., 2010). Additionally, a recent systematic review explored the role of the oxytocin system in fear extinction in rodents (Neumann and Slattery, 2016). The findings revealed that oxytocin reduced fear related behaviours and facilitated fear extinction in rodents, particularly when the exogenous oxytocin or oxytocin agonists were administered to the infralimbic cortex (Neumann and Slattery, 2016). The infralimbic cortex has inhibitory projections to a number of subcortical regions in the rodent brain including the amygdala and activation of this region has been documented to be associated with fear extinction in rodents and humans (Quirk and Beer, 2006). These findings suggest that oxytocin may reduce fear and facilitate extinction possibly by reducing stress and anxiety around the source of potential threat. Thus, these findings have led to increasing interest to investigate the role oxytocin plays in threat processing and fear extinction in humans as well as its therapeutic potential in disorders characterised by elevated threat sensitivity and resistance to natural extinction.

A few studies have begun to explore the effects of intranasal oxytocin on threat processing and the physiological stress and anxiety response in humans. For example a recent meta-analysis found that a single dose of intranasal oxytocin lowered cortisol in clinical populations characterised by dysregulation of the HPA axis, but did not significantly influence the cortisol response to stressful stimuli in healthy individuals (Cardoso et al., 2014). Since many psychiatric disorders, including ED, PTSD, and anxiety disorders, are characterised by dysregulation of the HPA axis (Connan et al., 2007; Ehlert et al., 2001; Lo Sauro et al., 2008), there has been increasing interest in further exploration of the potential anti-stress and anxiolytic effects of intranasal oxytocin in psychiatric disorders characterised by elevated threat sensitivity. To our knowledge, no systematic reviews have thus far investigated the effects of single dose of intranasal oxytocin on different aspects of threat processing in healthy and clinical populations more broadly.

The aim of the current systematic review and meta-analyses was to build on previous literature and synthesise studies examining the effects of a single dose of intranasal oxytocin on threat processing among in humans. The objective was to investigate the effects of oxytocin on the physiological startle response, behavioural approach and avoidance responses, and attentional responses, including attentional bias and fixation, towards generally threatening stimuli as well as towards disorder related threatening stimuli among clinical populations. Based on findings outlined above, we hypothesised that a single dose of intranasal oxytocin would reduce these anomalous threat responses in clinical populations characterised by elevated threat sensitivity.

3 Methodology

3.1 Literature search

In accordance with the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009), electronic databases, including OVID (PsycINFO, PsycARTICLES, Medline, ARGIS), Web of Knowledge core collection, and Pubmed, were searched April 2017. The search terms included *oxytocin AND (threat OR fear OR anxiety OR avoidance OR attention OR bias OR startle OR approach OR fixation OR gaze)*. Furthermore, bibliographies of included studies were inspected to look for further studies not yielded by the initial search.

3.2 Inclusion criteria

In order to be included in the systematic reviews and meta-analyses studies were required to meet the following inclusion criteria: 1) investigate physiological response, behavioural approach and avoidance response, attention, or fixation towards threatening or feared stimuli; 2) investigate the effects of a single dose of intranasal oxytocin on these measures; 3) compare the effects of intranasal oxytocin against intranasal placebo; 4) include healthy adult participants and/or adult clinical populations; 5) random allocation of participants to receive intranasal oxytocin or placebo in studies using between subjects design; 6) randomisation of treatment order in studies using within subjects design; 7) be published in English in a peer reviewed journal. In order to reduce heterogeneity, long trials in which participants received more than one dose of oxytocin or in which effects of oxytocin were investigated the following day or later were not included.

3.3 Study selection

The search flow diagram is presented in Figure 1. The literature search and initial screening based on title and abstract was conducted by the first author. The full text articles identified in the initial search and screening were examined for eligibility by two authors in conjunction (J.L. and K.W.N.). Studies were then included in the systematic review and meta-analyses if both authors agreed they met the inclusion criteria. If there was any uncertainty regarding eligibility of a paper it was referred to the rest of team for further discussion.

Figure 1. Literature search flow diagram

-----FIGURE 1-----

3.4 Data collection and synthesis

We conducted three separate meta-analyses investigating the effects of a single dose of intranasal oxytocin on the physiological response, behavioural approach and avoidance response, attention, and fixation towards threatening stimuli. To conduct these meta-analyses information regarding means, standard deviations, and sample size were extracted from the included articles. Where standard errors of the mean (SE) were reported instead of standard deviations, these were converted with the following formula: $SD = SE * \sqrt{N}$. Fourteen studies did report the data in the article or in supplementary materials, or reported the data in figures only. In order to acquire the required data, the corresponding authors of these papers were contacted by one of the authors. The relevant data was obtained from the following studies via personal communication: Acheson et al. (2013); Bertsch et al. (2013); Eckstein et al. (2015); Eckstein et al. (2016); Hubble et al. (2017); Kim et al. In prep; Leknes et al. (2013); Preckel et al. (2014); Striepens et al. (2012). Despite contacting corresponding authors, we were unable to gain access to the relevant data from eight studies.

In addition to healthy individuals, clinical populations included in the study consisted of people with anorexia nervosa (AN), bulimia nervosa (BN), depression, and BPD. Information regarding participants' age, dose of oxytocin (in international units), the type of task used, the stimulus presentation time in milliseconds (ms), the study design (between subjects, within subjects), and the proportion of female participants in the study, was also extracted from the articles for the purposes of meta-regression.

Where appropriate, information regarding psychopathology was extracted from the studies. This information was extracted from the three studies that investigated the effects of a single dose of intranasal oxytocin on attentional bias to disorder-specific stimuli. This information consisted of self-reported anxiety measured with the Depression, Anxiety and Stress Scale (DASS) and Spielberger State and the Trait Anxiety Inventory (STAI), self-reported depression measured with the DASS and Beck Depression Inventory (BDI), and self-reported ED psychopathology measured with the Eating Disorder Examination Questionnaire. Self-reported anxiety and depression scores were converted to standardised z-scores prior to being included in the meta-regression.

Finally, we also conducted a systematic review of studies investigating the effects of a single dose of oxytocin on behavioural approach and avoidance. We were not able to conduct a meta-analysis due to a small number of studies and differences in outcome measures used.

3.5 Tasks used to examine threat processing

3.5.1 Startle response

Seven studies investigated the effects of a single dose of intranasal oxytocin on the physiological response to general threat and learned threat (Table 1). Four studies investigated the effects of

intranasal oxytocin on the physiological response to generally threatening stimuli, including angry faces, images of threatening scenes, and predictable and unpredictable electric shocks (Grillon et al., 2013; Leknes et al., 2013; Prehn et al., 2013; Striepens et al., 2012). Three studies investigated the effects of oxytocin on startle response to learned threat cues after conditioning and on learned threat following extinction (Acheson et al., 2013; Eckstein et al., 2015; Eckstein et al., 2016). The outcomes measures included eye blink magnitude, skin conductance response, pupil dilation, and facial electromyography (EMG). All studies included only healthy individuals. One study reported data separately for male and female participants (Grillon et al., 2013).

3.5.2 Approach and avoidance responses

Five studies investigated the effects of a single dose of intranasal oxytocin on approach and avoidance responses to threatening images including angry faces and general negative stimuli (Table 1). In this experimental paradigm participants are presented with threatening and neutral stimuli one at a time and asked to respond either by pulling or pushing a lever as quickly as possible. Pushing the lever shrinks the stimulus on the screen indicating avoidance of the stimulus, whereas pulling the lever zooms in on the stimulus on the screen indicating approach towards the stimulus. One study reported approach reaction times (Preckel et al., 2014) and another study reported reaction times for both approach and avoidance responses (Radke et al., 2017). Two other studies reported approach-avoidance bias scores (Mitchell et al., 2016; Radke et al., 2013). Positive bias scores indicated approach and negative bias scores indicated avoidance. Finally, one study did not report the relevant data but provided test statistics (Theodoridou et al., 2013). Four of the studies only included healthy individuals, one included people with alcohol dependence disorder, and one explored the effects of oxytocin in low and highly anxious people. Effect sizes and confidence intervals are reported for the four studies that provided the relevant data.

3.5.3 Attentional responses

Two methods were used to investigate the effects of a single dose of intranasal oxytocin on attentional responses to threat: attentional bias towards threatening images relative to neutral images and fixation towards regions of interest within threatening images (Table 1). Seven studies investigated the effects of a single dose of intranasal oxytocin on attentional bias towards social threat, namely images of angry and disgusted faces. Six of the studies examined attentional bias using the dot-probe paradigm and one used a spatial cueing task. In these tasks participants are initially presented with a fixation cross followed by the presentation of a threatening stimulus either alone on one side of a computer screen or in combination with a neutral stimulus on opposite sides of the screen. After the threatening stimulus has disappeared, a target is presented either in the same place where the threatening stimulus was or on the opposite side of the screen. Participants are then asked to identify the target by pressing the appropriate key on a keyboard. In the dot-probe tasks attentional bias scores were calculated from the response times, subtracting response times in trials, where the probe replaced a neutral stimulus from response times in trials, where the probe replaced the threatening stimulus. Positive scores indicate increased attention towards the threatening stimuli while negative scores indicate reduced attention towards the threatening stimuli.

In the spatial cueing task attentional bias and avoidance were investigated separately by examining reaction times in congruent trials, in which the target was presented in the same side of the screen as the threatening image, and incongruent trials, in which the target was presented on the other side of the screen relative to the threatening image (Ellenbogen et al., 2012). The final attentional bias scores are calculated by subtracting response time in the congruent neutral trials from response times in the congruent threatening trials. The attentional avoidance scores are calculated by subtracting response time in the incongruent neutral trials from response times in the incongruent threatening trials. Thus, as above and despite different methods, positive scores

indicate increased attention towards the threatening stimuli and negative scores indicate reduced attention towards the threatening stimuli in both tasks. Further, two of the studies varied the cue presentation duration or used masked cue presentation (Brune et al., 2013; Domes et al., 2016; Ellenbogen et al., 2012).

Three studies investigated attentional bias towards disorder-specific threatening stimuli in ED, namely AN and BN, using the dot-probe paradigm (Table 1). These studies used food, body shape, and body weight related images as threatening stimuli. As above, positive attentional bias scores indicated greater attention towards the disorder-specific threatening images, and negative scores indicated attention away from the stimuli. One of the studies varied the cue presentation duration (Kim et al., In prep.), and another study investigated attentional bias with varied inter-trial interval (500ms or 1250ms) before and after a smoothie challenge (Leppanen et al., 2017).

Five studies investigated the effects of a single dose of intranasal oxytocin on attention towards regions of interest (ROIs) in threatening images using eye tracking (Table 1). Three of the studies defined the ROIs as the eye and mouth region of angry and disgusted faces (Bertsch et al., 2013; Domes et al., 2013; Hubble et al., 2017; Lischke et al., 2012a). One study investigated fixation towards predefined regions of interest in threatening scenes taken from the international picture affective system (Lischke et al., 2012b). The ROIs were predefined based on pilot data. The outcome measure was preferential fixation towards the ROIs relative to the rest of the face or the background of the image.

3.6 Statistical analysis

Statistical analyses were conducted with the Metafor package in R (R Core Team, 2015; Viechtbauer, 2010). For studies using between subjects design, standardised, unbiased effect sizes were

estimated by calculating Hedges' g (Hedges, 1981) and 95% confidence intervals. For studies using within subjects design standardised mean change with change score standardisation (SMCC) along with 95% confidence intervals was calculated. Where correlation between the two conditions was not reported to calculate the SMCC effect size estimate, the correlation was estimated using the following formula: $\frac{SD1^2 + SD2^2 - SD_{change}^2}{2 * SD1 * SD2}$ (Morris and DeShon, 2002). The Hedges' g and SMCC effect size estimates are both on the same scale and were interpreted as small (≥ 0.20), medium (≥ 0.50), and large (≥ 0.80). Positive effect sizes indicated oxytocin-induced increase in startle response, approach, and attention towards threatening stimuli. Negative effect sizes indicated oxytocin-induced reduction in startle response, approach, and attention towards threatening stimuli.

Because a number of studies used a variety of paradigms to investigate different aspects of threat processing, the same participants were included in a meta-analysis more than once. To account for confounding effects arising from this, we conducted multivariate meta-analyses with an autoregressive structure. Between-study heterogeneity was examined with the *Cochran's Q* index. Significant heterogeneity between studies was further investigated with meta-regressions to examine the moderating effects of the following variables: age, the study design, the dose administered (in IU), the type of task used, diagnosis, the type of stimuli used, and the proportion of female participants in the sample. Significance level was set at $p < 0.05$.

Presence of outliers was investigated by calculating standardised residuals of each study included in the meta-analyses. If the Z scores of the standardised residuals exceeded ± 1.96 , the study was deemed an influential outlier and was thus removed from the analyses (Viechtbauer and Cheung, 2010).

Publication bias based on funnel plot asymmetry was investigated with Begg's rank correlation test (Begg and Mazumdar, 1994). Additionally, where significant effects were present their robustness

was assessed with the Rosenthal's fail-safe N analysis (Rosenthal, 1979). The analysis provides a fail-safe number of studies with non-significant results that would need to be included for the effects to be reduced to null. The effect is considered robust if the fail-safe N exceeds the Rosenthal criterion, $5k+10$, where k is the number of studies included in the meta-analysis (Rosenthal, 1991).

Finally, we explored whether the included studies had large enough sample sizes to have adequate power to detect an effect of oxytocin on threat processing. According to the power analysis conducted with G*Power (Faul et al., 2007), between subjects studies should have at least 64 participants in each group and within subjects studies should have at least 34 participants, to have 80% power to detect a moderate effect.

4 Results

4.1 Study characteristics

Characteristics of the 26 included studies are presented in Table 1. The effect size (ES) column shows the standardised effect size estimate along with 95% confidence intervals for each study. The power column show whether the study had a sufficiently large sample size to have 80% power to detect at least a moderate ($ES \geq 0.5$) effect of oxytocin. Only one study using within subjects design met the sample size requirement of sufficient power. Six other studies using within subjects design came close to having sufficient power (sample size ≥ 30).

4.2 Effects of oxytocin on startle response to threat

The studies investigating the effects of a single dose of intranasal oxytocin on physiological startle response to general threat and learned threat are presented in Figure 2. Overall, the meta-analysis revealed that intranasal oxytocin significantly increased startle response to threat with a small effect

size (ES = 0.32, 95% CI [0.13, 0.52], $Z = 3.27$, $p = 0.001$). We further explored the effects of oxytocin on startle response to general threat and learned threat following conditioning. Intranasal oxytocin significantly increased startle response to general threat with a small effect size (ES = 0.30, 95% CI [0.07, 0.53], $Z = 2.55$, $p = 0.011$). Oxytocin-induced increase in startle response following conditioning also approached significance with a small effect size (ES = 0.41, 95% CI [-0.01, 0.82], $Z = 1.90$, $p = 0.058$).

There was no significant between-study heterogeneity ($Q = 11.32$, $p = 0.297$, $I^2 = 29.00$), and thus, no meta-regressions were conducted. Begg's rank correlation test based on the funnel plots did not indicate there was evidence of significant publication bias ($\tau = 0.24$, $p = 0.359$, Supplementary Figure 1). The Rosenthal's fail-safe N analysis revealed that 55 studies with non-significant results would need to be added to the present meta-analysis to reduce the observed effect to null. This exceeds the Rosenthal criterion ($55 > (5 \times 7 + 10) = 45$) suggesting that the effect observed was robust.

Figure 2. Forest plot of studies investigating the effects of intranasal oxytocin on the startle response to threat

-----FIGURE 2-----

Grillon et al. 2013(a) = female participants, Grillon et al. 2013(b) = male participants, Angry faces (f) = angry female faces, Angry faces (m) = angry male faces, EMG = electromyography.

4.3 Effects of oxytocin on attentional responses towards threat

4.3.1 Attentional bias towards social threat

The studies investigating the effects of a single dose of intranasal oxytocin on attentional bias towards social threat are presented in Figure 3. Overall, a single dose of intranasal oxytocin did not

significantly influence attentional bias towards social threat ($ES = -0.10$, 95% CI $[-0.50, 0.29]$, $Z = -0.51$, $p = 0.612$). We then further explored the effects within the healthy and clinical populations. Among the healthy individuals, oxytocin did not significantly impact attentional bias towards social threat ($ES = -0.42$, 95% CI $[-1.07, 0.23]$, $Z = -1.26$, $p = 0.208$). There was also no significant effects of oxytocin among the mixed clinical group ($ES = 0.13$, 95% CI $[-0.35, 0.61]$, $Z = 0.54$, $p = 0.593$).

The overall meta-analysis revealed significant between-study heterogeneity ($Q = 73.53$, $p < 0.001$), which was explored further with meta-regressions. Together the stimuli used, the stimulus presentation time, and the diagnostic group significantly moderated some of the between-study heterogeneity ($QM = 43.41$, $p < 0.0001$), still leaving significant residual heterogeneity ($QR = 24.60$, $p = 0.004$). This suggests that the effects of oxytocin on attentional bias were the strongest among highly anxious people and people with BPD when the angry faces were presented for 500ms or less time. However, only one study included people with BPD and only one study included highly anxious people and, thus, these findings should be interpreted with caution. The proportion of female participants in the study ($QM = 0.03$, $p = 0.859$), the study design ($QM = 0.11$, $p = 0.744$), age ($QM = 0.295$, $p = 0.589$), the task used ($QM = 0.29$, $p = 0.963$), and the dose administered ($QM = 0.01$, $p = 0.929$) did not significantly moderate the between study heterogeneity.

The Begg's rank correlation test based on the funnel plot asymmetry did not reveal evidence of significant publication bias ($\tau = 0.09$, $p = 0.565$; Supplementary figure 2).

Figure 3. Forest plot of studies investigating the effects of intranasal oxytocin on the attentional bias towards social threat

-----FIGURE 3-----

Ellenbogen et al. 2012 (a) = congruent trials, Ellenbogen et al. 2012 (b) = incongruent trials, AN = anorexia nervosa; BN = bulimia nervosa; BPD = borderline personality disorder, ms = milliseconds.

4.3.2 Attentional bias towards disorder-specific threat

The studies investigating the effects of a single dose of intranasal oxytocin on attentional bias towards disorder-specific threatening stimuli are presented in Figure 3. Only studies including people with ED, namely AN and BN, had investigated these effects. The disorder-specific threatening stimuli consisted of negative body shape related, body weight related, and food related images.

The meta-analysis showed that overall a single dose of intranasal oxytocin did not significantly influence attentional bias towards disorder-specific stimuli in eating disorders ($ES = -0.05$, 95% CI [-0.28, 0.18], $Z = -0.43$, $p = 0.670$). We further explored the effect of a single dose of oxytocin separately on the different types of disorder specific stimuli used. Intranasal oxytocin did not significantly influence attentional bias towards negative body shape related stimuli ($ES = -0.07$, 95% CI [-0.66, 0.52], $Z = -0.23$, $p = 0.818$), body weight related stimuli ($g = 0.09$, 95% CI [-0.12, 0.30], $Z = 0.86$, $p = 0.388$), or food related stimuli ($ES = -0.10$, 95% CI [-0.36, 0.15], $Z = -0.79$, $p = 0.429$).

There was significant between-study heterogeneity ($Q = 24.52$, $p = 0.017$), which was explored further with meta-regressions. Diagnostic group significantly explained the between-study heterogeneity ($QM = 6.37$, $p = 0.012$), still leaving some unaccounted heterogeneity that approached significance ($QR = 18.15$, $p = 0.078$). This suggests that people with BN showed greater oxytocin induced increase in attentional bias towards disorder-specific stimuli ($ES = 0.15$, 95% CI [-0.03, 0.33], $Z = 1.66$, $p = 0.096$), whereas people with AN showed greater oxytocin-induced increase in attentional avoidance of disorder-specific stimuli ($ES = -0.16$, 95% CI [-0.33, 0.03], $Z = -1.92$, $p = 0.055$). However, neither of these effects reached significance and only one study investigated the effects of oxytocin in people with BN. Therefore, these findings should be interpreted with caution. Self-reported anxiety ($QM = 0.20$, $p = 0.655$), self-reported depression ($QM = 1.41$, $p = 0.235$), self-

reported eating disorder symptomatology (QM = 0.04, $p = 0.846$), the stimuli used (QM = 1.56, $p = 0.458$), age (QM = 0.01, $p = 0.937$), and variations in the task used (QM = 0.08, $p = 0.995$) did not significantly moderate the between study heterogeneity. The proportion of female participants in the study, the dose administered, and the study design were not entered as predictors in the meta-regression as all included studies recruited only female participants, used the same within subjects design, and administered the same dose oxytocin.

The Begg's rank correlation test based on the funnel plot asymmetry did not reveal evidence of significant publication bias ($\tau = -0.15$, $p = 0.510$; Supplementary figure 3).

Figure 4. Forest plot of studies investigating the effects of intranasal oxytocin on attentional bias towards disorder specific threat

-----FIGURE 4-----
 Leppanen et al 2017 (a) = before smoothie challenge, Leppanen et al 2017 (b) = after smoothie challenge, AN = anorexia nervosa, BN = bulimia nervosa, ms = milliseconds, ITI = inter-trial interval.

4.3.3 Fixation towards regions of interest

The studies investigating the effects of a single dose of intranasal oxytocin on fixation towards ROIs in threatening images are presented in Figure 4. The meta-analysis showed that a single dose of oxytocin did not significantly influence fixation towards ROIs in threatening images ($g = -0.08$, 95% CI [-0.23, 0.08], $Z = -0.96$, $p = 0.339$).

There was significant between-study heterogeneity ($Q = 22.65$, $p = 0.031$), which was explored further with meta-regressions. The ROI used (QM = 1.53, $p = 0.465$), age (QM = 0.01, $p = 0.931$), the

proportion of female participants in the study (QM = 0.28, $p = 0.597$), the study design (QM = 0.65, $p = 0.419$), the task used (QM = 1.53, $p = 0.216$), how fixation was measured (QM = 3.02, $p = 0.388$), the type of stimuli used (QM = 2.87, $p = 0.238$), the diagnosis (QM = 1.80, $p = 0.179$), and the dose administered (QM = 0.25, $p = 0.615$) did not significantly moderate the heterogeneity.

Begg's rank correlation test based on the funnel plots did not reveal any significant publication bias ($\tau = -0.17$, $p = 0.435$, Supplementary Figure 4).

Figure 5. Forest plot of studies investigating the effects of intranasal oxytocin on fixation towards regions of interest in threatening images

-----FIGURE 5-----

ROI = region of interest, BPD = borderline personality disorder. Lischke et al 2012a used predefined regions of interest based on pilot data.

4.4 Effects of oxytocin on approach and avoidance responses to threat

It was not possible to conduct a full meta-analysis of the studies investigating the effects of oxytocin on approach and avoidance responses due to the small number of studies and the variety of different outcome measures used. The significance of the findings from each study was then investigated by examining the 95% confidence intervals of the effect size estimates according to the guidelines stated in the Cochrane Handbook for Systematic Reviews (Higgins and Green, 2011).

Two studies used a between subjects design to investigate the effects of a single dose of intranasal oxytocin on approach and avoidance reaction times (Preckel et al., 2014; Radke et al., 2017). The study by Preckel et al. (2014) examined only approach reaction times to social and non-social threat. The study found that intranasal oxytocin led to a small reduction in reaction times when approaching threatening social stimuli (ES = 0.34, 95% CI [-0.14, 0.83], total N = 67). There was a

negligible reduction in reaction times when approaching non-social threatening stimuli ($ES = 0.07$, 95% CI $[-0.41, 0.55]$, total $N = 67$). However, in both cases the 95% confidence intervals overlapped zero indicating that neither effect was statistically significant. Conversely, Radke et al. (2017) found that oxytocin led to a non-significant increase in approach reaction times towards social threat with a moderate effect size ($ES = -0.51$, 95% CI $[-1.07, 0.04]$, total $N = 52$), and a significant increase in avoidance reaction times with a moderate effect size ($ES = -0.56$, 95% CI $[-1.11, -0.002]$, total $N = 52$). These contradictory findings may be some way explained by the differences in sample size.

Two studies by Radke et al. (2013) and Mitchell et al. (2016) used within subjects design to investigate approach/avoidance bias in healthy people and people with alcohol dependence disorder respectively. Radke et al. (2013) found a significant oxytocin-induced increase in approach bias towards threatening social stimuli with a moderate effect size among healthy individuals ($ES = 0.52$, 95% CI $[0.09, 0.95]$, $N = 24$). Similarly, Mitchell et al. (2016) found a negligible oxytocin-induced increase in approach bias towards threatening non-social stimuli in people with alcohol dependence disorder ($ES = 0.16$, 95% CI $[-0.19, 0.51]$, $N = 32$), although this did not reach significance. Taken together these findings suggest that oxytocin may increase approach bias towards threatening stimuli, particularly threatening social stimuli. However, further research is needed to confirm this finding.

Finally, the study by Theodoridou et al. (2013) used a between subjects design to investigate the effects of intranasal oxytocin on both approach and avoidance responses to social threat (total $N = 120$). The authors did not report the relevant data to allow effect sizes to be calculated, but reported test statistics that showed no significant effect of intranasal oxytocin on approach or avoidance responses (Theodoridou et al., 2013).

Taken together these studies indicate that there is uncertainty about the effects of intranasal oxytocin on approach and avoidance responses to threatening stimuli. Indeed, the 95% confidence interval ranges in all studies were very wide (Higgins and Green 2011). Still, there was some indication that oxytocin may influence approach responses to threatening stimuli, particularly social threat. However, it is of interest that the two studies that showed significant effect size estimates also had smaller sample sizes (within subjects $N = 24$; between subjects $N = 52$) than the other studies reporting no significant effects of oxytocin (within subjects $N = 32$, between subjects $N = 67 - 120$). Thus, further research with larger samples is needed.

5 Discussion

The aim of the present review was to examine the effects of a single dose of intranasal oxytocin on threat processing in healthy and clinical populations. The majority of the studies included only healthy individuals and no studies investigated the influence of intranasal oxytocin on the physiological startle response among clinical populations. The findings revealed that intranasal oxytocin significantly increased the startle response to threatening stimuli in healthy individuals with a small effect size. However, a single dose of intranasal oxytocin did not significantly influence attentional bias towards social threat or disorder specific threat, or fixation to regions of interest in threatening stimuli. The findings for effects of a single dose of oxytocin on approach and avoidance responses towards threat were inconsistent, calling for further research with large samples. Moreover, a single dose of intranasal oxytocin did not significantly influence attentional bias to social or disorder-specific threat among the clinical populations.

In preclinical studies, oxytocin has been shown to facilitate extinction and generally inhibit anxiety- and fear-related responses and behaviours in rodents (Calcagnoli et al., 2015; Huber et al., 2005; Neumann and Slattery, 2016; Viviani et al., 2011). Conversely, the present review did not find

evidence of significant overall effects of intranasal oxytocin on attentional or behavioural approach or avoidance responses to threat in humans. Instead, we found that a single dose of intranasal oxytocin significantly increased startle response to threatening stimuli in healthy individuals. Based on the present findings, in healthy humans, oxytocin appears to primarily influence the salience of threatening stimuli, possibly indicating that oxytocin plays a role in arousal but not behavioural responding in humans. This interpretation is supported by findings from recent neuroimaging studies investigating neural responses to social threat in healthy humans. These studies have reported oxytocin-induced increases in neural activation in regions, including the amygdala, which are associated with processing of salience and arousal (Frijling et al., 2016; Gorka et al., 2015; Koch et al., 2016). This interpretation is further supported by findings from a previous meta-analysis that found that a single dose of intranasal oxytocin improved early detection of anger and late detection of fear in healthy humans (Shahrestani et al., 2013). Furthermore, a recent meta-analytic review by our group found that a single dose of oxytocin improved recognition of basic emotions, primarily fear and disgust, among healthy individuals (Leppanen et al., 2017). Thus, these findings suggest that rather than having global effects on threat processing, oxytocin may influence specific aspects of threat processing, such as arousal.

Regarding clinical populations, the present review found that a single dose of intranasal oxytocin did not significantly influence attentional bias towards social threat among clinical populations. These findings are somewhat surprising considering the number of systematic reviews suggesting that oxytocin may be an effective new target for treatments in psychiatric disorders alleviating psychopathology in a number of disorders (Bakermans-Kranenburg and van Ijzendoorn, 2013; MacDonald and Feifel, 2013; MacDonald and MacDonald, 2010; Meyer-Lindenberg et al., 2011). One possible interpretation of the present findings is that although it may be effective in targeting certain symptoms, intranasal oxytocin may have little effect on threat processing among the clinical

populations. This interpretation is in line with findings from recent work investigating the effectiveness of intranasal oxytocin as a treatment enhancer in depression and BPD, which found that intranasal oxytocin did not improve anxiety or affiliative behaviour during therapy or clinical interview (Brune et al., 2015; MacDonald et al., 2013). Additionally, another study found that intranasal oxytocin did not improve self-reported anxiety among people with social anxiety disorder following exposure therapy (Guastella et al., 2009).

It is of note, however, that the present review was only able to investigate the effects of a single dose of intranasal oxytocin attentional responses to threat among clinical populations due to lack of studies. Thus, it is possible that intranasal oxytocin does not have a significant effect on threat related attentional or behavioural responses, but may modulate other aspects of threat processing among clinical population. Indeed, a previous meta-analysis found that a single dose of oxytocin reduced the cortisol response to stressful stimuli among clinical populations (Cardoso et al., 2014). Similarly, a recent systematic review reported that intranasal oxytocin may be effective in combating anxiety and stress in disorder characterised by dysfunction of the central nervous system (Chapman et al., 2013). Furthermore, a recent experimental study found that a single dose of oxytocin increased heart rate response to trauma related stimuli while reducing self-reported trauma-related imagery among people with PTSD (Sack et al., 2017). These findings suggest that oxytocin may increase arousal while lowering stress and anxiety responses to threatening stimuli among clinical populations. However, further research with larger samples is still needed.

Another possible interpretation of the present findings is that there is substantial heterogeneity within and between clinical groups that could dilute the true effects of intranasal oxytocin on social threat processing among clinical populations (Lamers et al., 2010; Melartin et al., 2002; Wessman et al., 2009). Indeed, in the present study there was significant between study heterogeneity in the meta-analysis investigating effects of oxytocin on attentional bias towards threat among clinical

populations. Findings from preclinical and human studies also suggest that the effects of oxytocin may be mediated by baseline levels of anxiety and other individual differences, such as attachment difficulties (Bartz et al., 2011; Bosch et al., 2005; Olff et al., 2013; Zik and Roberts, 2015). Environmental differences, such as the conditions under which participants are tested, have also been suggested to influence the effects of oxytocin (Bartz et al., 2011; Olff et al., 2013). This suggestion is in line with findings from our previous single dose study, which found that the effects of intranasal oxytocin on attentional bias towards food images in people with AN was dependent not only on whether the task was delivered before or after a smoothie challenge, but also on the inter-trial interval used in the task (Leppanen et al., 2017). Although, further research could help gain better understanding of the effects of intranasal oxytocin on threat processing among clinical populations, these findings raise some questions about the therapeutic potential and effectiveness of intranasal oxytocin in the treatment of psychiatric disorders.

5.1 Limitations and future directions

The main limitation of this review is the small number of studies investigating the effects of intranasal oxytocin on different aspects of threat processing. Indeed, there were so few studies investigating the effects of a single dose of intranasal oxytocin on behavioural approach and avoidance responses to threatening stimuli, we were not able to conduct a full meta-analysis. Furthermore, only one of the studies reviewed here met our sample size requirement for adequate statistical power. These limitations were an issue when reviewing studies investigating the effects of a single dose of oxytocin on approach and avoidance responses. The only two that showed significant effects of oxytocin had smaller sample size than the other similar studies that did not show significant effects of oxytocin. It is possible that these findings were driven by the fact that smaller studies can sometimes overestimate effect sizes even when no true effect is present (Walum

et al., 2016; Zhang et al., 2013). These findings suggest that this is still a relatively unexplored field, and as further research with larger samples is needed.

Additionally, there is relative paucity of research investigating the effects a single dose of intranasal oxytocin on threat processing among clinical populations. In the present review we were only able to investigate the effects of a single dose of oxytocin on attentional bias towards threat among clinical populations, but not the physiological startle response, approach and avoidance responses, or fixation response due to a lack of studies. Further research is needed to shed light on the effects of oxytocin on elevated threat sensitivity in psychiatric disorders.

The dot-probe and spatial cueing tasks that were used to examine the effects of oxytocin on attention to social threat demonstrated that variation of task parameters, such as stimulus presentation time and inter-trial interval, had an impact on the effects of oxytocin. These factors added heterogeneity into the meta-analyses and influenced the interpretation of the findings. Short stimulus presentation duration is believed to tap into early attentional responses while longer stimulus duration is believed to examine late attention (Bantin et al., 2016). However, there are still some uncertainties regarding what should be used as the cut-off for early and late attention, with some eye tracking and electroencephalogram (EEG) studies reporting attentional shifts as early as 200ms after stimulus onset (Bantin et al., 2016; Belyusar et al., 2013; Hedge and Leonards, 2013). Additionally, working memory and executive functioning studies have demonstrated that varying the inter-trial interval can impact performance, with shorter inter-trial intervals utilising more automated responding, while longer inter-trial intervals allow for more controlled responding (Cermak, 1970; Shipstead and Engle, 2013). Thus, to avoid these issues, future studies may benefit from utilising other methods to assess attentional bias, such as eye tracking or EEG, and working towards developing standardised measures.

Finally, there was significant between study heterogeneity in the meta-analysis investigating the effects of a single dose of oxytocin on attentional bias towards social threat and disorder-specific threat. Despite conducting meta-regressions to investigate moderating effects of age, dose, the type of task used, the type of stimuli used, and study design, we were not able to ascertain the source of the heterogeneity. Factors such as anxiety, attachment style, and alexithymia have been found to influence the effects of oxytocin on a number of different tasks (Bartz et al., 2011; Bosch et al., 2005; Olf et al., 2013; Zik and Roberts, 2015). However, since these variables were not explored or reported in the included studies we were unable to explore their moderator effects in the present review. Thus, further work investigating potential moderators of the effects of oxytocin on attentional bias towards threatening stimuli would be of interest.

6 Conclusions

The aim of the present review was to examine the effects of a single dose of intranasal oxytocin on threat processing in healthy and clinical populations. The findings revealed that oxytocin significantly increased the physiological startle response to threat in healthy people with a small effect size. Oxytocin did not have significant effects on attentional bias towards social or disorder-specific threat or on fixation towards threatening stimuli among healthy or clinical populations. There was also no convincing evidence that oxytocin significantly influences threat related behavioural approach or avoidance responses. These findings suggest that oxytocin may primarily influence the salience of threatening stimuli possibly indicating that oxytocin plays a role in emotional, but not behavioural processing in humans. Large scale research investigating the effects of oxytocin on physiological startle response among clinical populations would be of interest.

Author Disclosure

Contributors:

JL: Made substantial contributions to conception and design of the review, conducted literature search, screened search output, extracted data, analysed data, participated in writing the article

KWN: Made substantial contributions to conception and design of the review, screened search output, extracted data, participated in drafting and critically revising the article

YK: Made substantial contributions to conception and design of the review, participated in critically revising the article

KT: Made substantial contributions to conception and design of the review, participated in critically revising the article

JT: Made substantial contributions to conception and design of the review, participated in drafting and critically revising the article

All authors have approved the final article

Role of funding source:

The funding sources had no involvement or role in the design; in the collection, analysis and interpretation of the data; in the writing of the article; or in the decision to submit the article for publication.

Conflict of Interest: None

7 Acknowledgements

This study was supported by The Swiss Anorexia Nervosa Foundation [CSP Ref: 82905] and Guy's and St. Thomas' Charity [Ref: R1405174]. JL is supported by a scholarship from the Psychiatry Research Trust. KWN is supported by Singapore General Hospital. KT received funding from Swiss Anorexia Foundation [Protocol #58-16]. JT receives salary support from the National Institute for Health Research (NIHR), Mental Health Biomedical Research at South London and Maudsley NHS Foundation Trust, and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

The authors do not report any financial or non-financial conflicting interests.

8 References

- Acheson, D., Feifel, D., de Wilde, S., McKinney, R., Lohr, J., Risbrough, V., 2013. The effect of intranasal oxytocin treatment on conditioned fear extinction and recall in a healthy human sample. *Psychopharmacology* 229, 199-208.
- Altman, S.E., Campbell, M.L., Nelson, B.D., Faust, J.P., Shankman, S.A., 2013. The relation between symptoms of bulimia nervosa and obsessive-compulsive disorder: A startle investigation. *J. Abnorm. Psychol.* 122, 1132-1141.
- Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., 2013. Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. *Transl. Psychiatry.* 3, e258.
- Bantin, T., Stevens, S., Gerlach, A.L., Hermann, C., 2016. What does the facial dot-probe task tell us about attentional processes in social anxiety? A systematic review. *J. Behav. Ther. Exp. Psychiatry.* 50, 40-51.
- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M.J., Van Ijzendoorn, M.H., 2007. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychol. Bull.* 133, 1.
- Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N., 2011. Social effects of oxytocin in humans: context and person matter. *Trends. Cogn. Sci.* 15, 301-309.
- Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1088-1101.
- Belyusar, D., Snyder, A.C., Frey, H.-P., Harwood, M.R., Wallman, J., Foxe, J.J., 2013. Oscillatory Alpha-Band Suppression Mechanisms during the Rapid Attentional Shifts Required to Perform an Anti-Saccade Task. *NeuroImage* 65, 395-407.
- Bertsch, K., Gamer, M., Schmidt, B., Schmidinger, I., Walther, S., Kastel, T., Schnell, K., Buchel, C., Domes, G., Herpertz, S.C., 2013. Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *Am. J. Psychiatry.* 170, 1169-1177.

- Bosch, O.J., Meddle, S.L., Beiderbeck, D.I., Douglas, A.J., Neumann, I.D., 2005. Brain Oxytocin Correlates with Maternal Aggression: Link to Anxiety. *J. Neurosci.* 25, 6807-6815.
- Britton, J.C., Lissek, S., Grillon, C., Norcross, M.A., Pine, D.S., 2011. Development of anxiety: the role of threat appraisal and fear learning. *Depress. Anxiety.* 28, 5-17.
- Broderick, J., Grisham, J.R., Weidemann, G., 2013. Disgust and Fear Responding in Contamination-Based Obsessive-Compulsive Disorder During Pictorial Exposure. *Behav. Ther.* 44, 27-38.
- Brooks, S., Prince, A., Stahl, D., Campbell, I.C., Treasure, J., 2011. A systematic review and meta-analysis of cognitive bias to food stimuli in people with disordered eating behaviour. *Clin. Psychol. Rev.* 31, 37-51.
- Brune, M., Ebert, A., Kolb, M., Tas, C., Edel, M.A., Roser, P., 2013. Oxytocin influences avoidant reactions to social threat in adults with borderline personality disorder. *Hum. Psychopharmacol.* 28, 552-561.
- Brune, M., Kolb, M., Ebert, A., Roser, P., Edel, M.A., 2015. Nonverbal Communication of Patients With Borderline Personality Disorder During Clinical Interviews A Double-Blind Placebo-Controlled Study Using Intranasal Oxytocin. *J. Nerv. Ment. Dis.* 203, 107-111.
- Calcagnoli, F., Stubbendorff, C., Meyer, N., de Boer, S.F., Althaus, M., Koolhaas, J.M., 2015. Oxytocin microinjected into the central amygdaloid nuclei exerts anti-aggressive effects in male rats. *Neuropharmacology* 90, 74-81.
- Cardoso, C., Kingdon, D., Ellenbogen, M.A., 2014. A meta-analytic review of the impact of intranasal oxytocin administration on cortisol concentrations during laboratory tasks: Moderation by method and mental health. *Psychoneuroendocrinology* 49, 161-170.
- Cavanaugh, J., Carp, S.B., Rock, C.M., French, J.A., 2016. Oxytocin modulates behavioral and physiological responses to a stressor in marmoset monkeys. *Psychoneuroendocrinology* 66, 22-30.
- Cermak, L.S., 1970. Decay of interference as a function of the intertrial interval in short-term memory. *J. Exp. Psychol. Gen.* 84, 499-501.

- Chapman, C.D., Frey, W.H., 2nd, Craft, S., Danielyan, L., Hallschmid, M., Schioth, H.B., Benedict, C., 2013. Intranasal treatment of central nervous system dysfunction in humans. *Pharm. Res.* 30, 2475-2484.
- Cisler, J.M., Koster, E.H.W., 2010. Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin. Psychol. Rev.* 30, 203-216.
- Clark-Elford, R., Nathan, P.J., Auyeung, B., Mogg, K., Bradley, B.P., Sule, A., Muller, U., Dudas, R.B., Sahakian, B.J., Baron-Cohen, S., 2015. Effects of Oxytocin on Attention to Emotional Faces in Healthy Volunteers and Highly Socially Anxious Males. *Int. J. Neuropsychopharmacol.* 18.
- Connan, F., Lightman, S.L., Landau, S., Wheeler, M., Treasure, J., Campbell, I.C., 2007. An investigation of hypothalamic-pituitary-adrenal axis hyperactivity in anorexia nervosa: the role of CRH and AVP. *J. Psychiatr. Res.* 41, 131-143.
- Domes, G., Normann, C., Heinrichs, M., 2016. The effect of oxytocin on attention to angry and happy faces in chronic depression. *BMC psychiatry.* 16.
- Domes, G., Steiner, A., Porges, S.W., Heinrichs, M., 2013. Oxytocin differentially modulates eye gaze to naturalistic social signals of happiness and anger. *Psychoneuroendocrinology* 38, 1198-1202.
- Eckstein, M., Becker, B., Scheele, D., Scholz, C., Preckel, K., Schlaepfer, T.E., Grinevich, V., Kendrick, K.M., Maier, W., Hurlemann, R., 2015. Oxytocin facilitates the extinction of conditioned fear in humans. *Biol. Psychiatry.* 78, 194-202.
- Eckstein, M., Scheele, D., Patin, A., Preckel, K., Becker, B., Walter, A., Domschke, K., Grinevich, V., Maier, W., Hurlemann, R., 2016. Oxytocin Facilitates Pavlovian Fear Learning in Males. *Neuropsychopharmacology* 41, 932-939.
- Ehlert, U., Gaab, J., Heinrichs, M., 2001. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus–pituitary–adrenal axis. *Biol. Psychiatry.* 57, 141-152.

- Ellenbogen, M.A., Linnen, A.M., Grumet, R., Cardoso, C., Joobar, R., 2012. The acute effects of intranasal oxytocin on automatic and effortful attentional shifting to emotional faces. *Psychophysiology*. 49, 128-137.
- Faul, F., Erdfelder, E., Lang, A.-G., Buchner, A., 2007. G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods*. 39, 175-191.
- Frijling, J.L., van Zuiden, M., Koch, S.B.J., Nawijn, L., Veltman, D.J., Olff, M., 2016. Effects of intranasal oxytocin on amygdala reactivity to emotional faces in recently trauma-exposed individuals. *Soc. Cogn. Affect. Neurosci*. 11, 327-336.
- Gorka, S.M., Fitzgerald, D.A., Labuschagne, I., Hosanagar, A., Wood, A.G., Nathan, P.J., Phan, K., 2015. Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. *Neuropsychopharmacology*. 40, 278-286.
- Grillon, C., Krinsky, M., Charney, D.R., Vytal, K., Ernst, M., Cornwell, B., 2013. Oxytocin increases anxiety to unpredictable threat. *Mol. Psychiatry*. 18, 958-960.
- Guastella, A.J., Howard, A.L., Dadds Mark, R., Mitchell, P., Carson, D.S., 2009. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. *Psychoneuroendocrinology*. 34, 917-923.
- Hedge, C., Leonards, U., 2013. Using eye movements to explore switch costs in working memory. *J. Vis*. 13, 18-18.
- Hedges, L.V., 1981. Distribution Theory for Glass's Estimator of Effect size and Related Estimators. *J. Educ. Behav. Stat*. 6, 107-128.
- Higgins, J.P.T., Green, S., 2011. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. The Cochrane Collaboration.
- Hubble, K., Daughters, K., Manstead, A.S., Rees, A., Thapar, A., van Goozen, S.H., 2017. Oxytocin Reduces Face Processing Time but Leaves Recognition Accuracy and Eye-Gaze Unaffected. *J. Int. Neuropsychol. Soc*. 23, 23-33.

- Huber, D., Veinante, P., Stoop, R., 2005. Vasopressin and Oxytocin Excite Distinct Neuronal Populations in the Central Amygdala. *Science*. 308, 245-248.
- Kim, Y.R., Kim, C.H., Cardi, V., Eom, J.S., Seong, Y., Treasure, J., 2014c. Intranasal oxytocin attenuates attentional bias for eating and fat shape stimuli in patients with anorexia nervosa. *Psychoneuroendocrinology*. 44, 133-142.
- Kim, Y.R., Kim, C.H., Park, J.H., Pyo, J., Treasure, J., 2014a. The impact of intranasal oxytocin on attention to social emotional stimuli in patients with anorexia nervosa: a double blind within-subject cross-over experiment. *PloS one*. 9, e90721.
- Kim, Y.R., Oh, S.M., Corfield, F., Jeong, D.W., Jang, E.Y., Treasure, J., 2014b. Intranasal oxytocin lessens the attentional bias to adult negative faces: A double blind within-subject experiment. *Psychiatry. Investig.* 11, 160-166.
- Koch, S.B., van Zuiden, M., Nawijn, L., Frijling, J.L., Veltman, D.J., Olff, M., 2016. Intranasal Oxytocin Administration Dampens Amygdala Reactivity towards Emotional Faces in Male and Female PTSD Patients. *Neuropsychopharmacology*. 41, 1495-1504.
- Lamers, F., de Jonge, P., Nolen, W.A., Smit, J.H., Zitman, F.G., Beekman, A.T., Penninx, B.W., 2010. Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). *J. Clin. Psychiatry*. 71, 1582-1589.
- Leknes, S., Wessberg, J., Ellingsen, D.M., Chelnokova, O., Olausson, H., Laeng, B., 2013. Oxytocin enhances pupil dilation and sensitivity to 'hidden' emotional expressions. *Soc. Cogn. Affect. Neurosci.* 8, 741-749.
- Leppanen, J., Cardi, V., Ng, K.W., Paloyelis, Y., Stein, D., Tchanturia, K., Treasure, J., 2017. The effects of intranasal oxytocin on smoothie intake, cortisol and attentional bias in anorexia nervosa. *Psychoneuroendocrinology*. 79, 167-174.
- Leppanen, J., Ng, K.W., Tchanturia, K., Treasure, J., 2017. Meta-analysis of the effects of intranasal oxytocin on interpretation and expression of emotions. *Neurosci. Biobehav. Rev.* 78, 125-144.

- Lischke, A., Berger, C., Prehn, K., Heinrichs, M., Herpertz, S.C., Domes, G., 2012b. Intranasal oxytocin enhances emotion recognition from dynamic facial expressions and leaves eye-gaze unaffected. *Psychoneuroendocrinology* 37, 475-481.
- Lischke, A., Gamer, M., Berger, C., Grossmann, A., Hauenstein, K., Heinrichs, M., Herpertz, S.C., Domes, G., 2012a. Oxytocin increases amygdala reactivity to threatening scenes in females. *Psychoneuroendocrinology* 37, 1431-1438.
- Lo Sauro, C., Raval di, C., Cabras, P.L., Faravelli, C., Ricca, V., 2008. Stress, Hypothalamic-Pituitary-Adrenal Axis and Eating Disorders. *Neuropsychobiology* 57, 95-115.
- MacDonald, K., Feifel, D., 2013. Helping oxytocin deliver: Considerations in the development of oxytocin-based therapeutics for brain disorders. *Front. Neurosci.* 15, 7, 35.
- MacDonald, K., MacDonald, T.M., 2010. The peptide that binds: A systematic review of Oxytocin and its prosocial effects in humans. *Harv. Rev. Psychiatry.* 18, 1-21.
- MacDonald, K., MacDonald, T.M., Brune, M., Lamb, K., Wilson, M.P., Golshan, S., Feifel, D., 2013. Oxytocin and psychotherapy: a pilot study of its physiological, behavioral and subjective effects in males with depression. *Psychoneuroendocrinology* 38, 2831-2843.
- Mauler, B.I., Hamm, A.O., Weike, A.I., Tuschen-Caffier, B., 2006. Affect regulation and food intake in bulimia nervosa: Emotional responding to food cues after deprivation and subsequent eating. *J. Abnorm. Psychol.* 115, 567.
- Melartin, T.K., Rytsala, H.J., Leskela, U.S., Lestela-Mielonen, P.S., Sokero, T.P., Isometsa, E.T., 2002. Current comorbidity of psychiatric disorders among DSM-IV major depressive disorder patients in psychiatric care in the Vantaa Depression Study. *J. Clin. Psychiatry.* 63, 126-134.
- Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M., 2011. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat. Rev. Neurosci.* 12, 524-538.
- Mitchell, J.M., Arcuni, P.A., Weinstein, D., Woolley, J.D., 2016. Intranasal Oxytocin Selectively Modulates Social Perception, Craving, and Approach Behavior in Subjects With Alcohol Use Disorder. *J. Addict. Med.* 10, 182-189.

- Morris, S.B., DeShon, R.P., 2002. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol. Methods*. 7, 105-125.
- Neumann, I.D., Slattery, D.A., 2016. Oxytocin in General Anxiety and Social Fear: A Translational Approach. *Biol. Psychiatry*. 79, 213-221.
- Öhman, A., 2005. The role of the amygdala in human fear: Automatic detection of threat. *Psychoneuroendocrinology* 30, 953-958.
- Öhman, A., 2007. Fear, *Encyclopedia of Stress*. Academic Press, New York, pp. 15-19.
- Olf, M., Frijling, J.L., Kubzansky, L.D., Bradley, B., Ellenbogen, M.A., Cardoso, C., Bartz, J.A., Yee, J.R., van Zuiden, M., 2013. The role of oxytocin in social bonding, stress regulation and mental health: An update on the moderating effects of context and interindividual differences. *Psychoneuroendocrinology* 38, 1883-1894.
- Onaka, T., Takayanagi, Y., Yoshida, M., 2012. Roles of Oxytocin Neurones in the Control of Stress, Energy Metabolism, and Social Behaviour. *J. Neuroendocrinol.* 24, 587-598.
- Ozawa, T., Johansen, Joshua P., 2014. Neural Circuits: Interacting Interneurons Regulate Fear Learning. *Curr. Biol.* 24, R690-R693.
- Parr, L.A., Modi, M., Siebert, E., Young, L.J., 2013. Intranasal oxytocin selectively attenuates rhesus monkeys' attention to negative facial expressions. *Psychoneuroendocrinology* 38, 1748-1756.
- Pitman, R.K., Rasmusson, A.M., Koenen, K.C., Shin, L.M., Orr, S.P., Gilbertson, M.W., Milad, M.R., Liberzon, I., 2012. Biological studies of post-traumatic stress disorder. *Nat. Rev. Neurosci.* 13, 769-787.
- Preckel, K., Scheele, D., Kendrick, K.M., Maier, W., Hurlemann, R., 2014. Oxytocin facilitates social approach behavior in women. *Front. Behav. Neurosci.* 8.
- Prehn, K., Kazzer, P., Lischke, A., Heinrichs, M., Herpertz, S.C., Domes, G., 2013. Effects of intranasal oxytocin on pupil dilation indicate increased salience of socioaffective stimuli. *Psychophysiology* 50, 528-537.

- Quirk, G.J., Beer, J.S., 2006. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. *Curr. Opin. Neurobiol.* 16, 723-727.
- R Core Team, 2015. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
- Radke, S., Roelofs, K., de Bruijn, E.R., 2013. Acting on anger: social anxiety modulates approach-avoidance tendencies after oxytocin administration. *Psychol. Sci.* 24, 1573-1578.
- Radke, S., Volman, I., Kokal, I., Roelofs, K., de Bruijn, E.R.A., Toni, I., 2017. Oxytocin reduces amygdala responses during threat approach. *Psychoneuroendocrinology*.
- Rosenthal, R., 1979. The file drawer problem and tolerance for null results. *Psychol. Bul.* 86, 638-641.
- Rosenthal, R., 1991. *Meta-analytic Procedures for Social Research*. Sage Publications, Newbury Park.
- Rotzinger, S., Lovejoy, D.A., Tan, L.A., 2010. Behavioral effects of neuropeptides in rodent models of depression and anxiety. *Peptides*. 31, 736-756.
- Sack, M., Spieler, D., Witzelmann, L., Eppe, G., Stich, J., Zaba, M., Schmidt, U., 2017. Intranasal oxytocin reduces provoked symptoms in female patients with posttraumatic stress disorder despite exerting sympathomimetic and positive chronotropic effects in a randomized controlled trial. *BMC Med.* 15, 40.
- Shahrestani, S., Kemp, A.H., Guastella, A.J., 2013. The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: A meta-analysis. *Neuropsychopharmacology*. 38, 1929-1936.
- Shipstead, Z., Engle, R.W., 2013. Interference within the focus of attention: working memory tasks reflect more than temporary maintenance. *Journal of experimental psychology. Learn. Mem. Cogn.* 39, 277-289.
- Simon, D., Kaufmann, C., Kniesche, R., Kischkel, E., Kathmann, N., 2013. Autonomic responses and neural-cardiac coupling during individually tailored symptom provocation in obsessive-compulsive disorder. *J. Anxiety. Disord.* 27, 635-644.

- Soussignan, R., Schaal, B., Rigaud, D., Royet, J.-P., Jiang, T., 2011. Hedonic reactivity to visual and olfactory cues: Rapid facial electromyographic reactions are altered in anorexia nervosa. *Biol. Psychol.* 86, 265-272.
- Striepens, N., Scheele, D., Kendrick, K.M., Becker, B., Schafer, L., Schwalba, K., Reul, J., Maier, W., Hurlemann, R., 2012. Oxytocin facilitates protective responses to aversive social stimuli in males. *Proc. Natl. Acad. Sci. U S A.* 109, 18144-18149.
- Strober, M., Freeman, R., Lampert, C., Diamond, J., 2007. The association of anxiety disorders and obsessive compulsive personality disorder with anorexia nervosa: Evidence from a family study with discussion of nosological and neurodevelopmental implications. *Int. J. Eat. Disord.* 40, S46-S51.
- Theodoridou, A., Penton-Voak, I.S., Rowe, A.C., 2013. A direct examination of the effect of intranasal administration of oxytocin on approach-avoidance motor responses to emotional stimuli. *PloS one.* 8, e58113.
- Uher, R., Murphy, T., Brammer, M.J., Dalgleish, T., Phillips, M.L., Ng, V.W., Andrew, C.M., Williams, S.C.R., Campbell, I.C., Treasure, J., 2004. Medial Prefrontal Cortex Activity Associated With Symptom Provocation in Eating Disorders. *Am. J. Psychiatry.* 161, 1238-1246.
- Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor package. *J. Stat. Softw.* 36, 1-48.
- Viechtbauer, W., Cheung, M.W.L., 2010. Outlier and influence diagnostics for meta-analysis. *Res. Synth. Methods.* 1, 112-125.
- Viviani, D., Charlet, A., van den Burg, E., Robinet, C., Hurni, N., Abatis, M., Magara, F., Stoop, R., 2011. Oxytocin Selectively Gates Fear Responses Through Distinct Outputs from the Central Amygdala. *Science.* 333, 104-107.
- Walum, H., Waldman, I.D., Young, L.J., 2016. Statistical and Methodological Considerations for the Interpretation of Intranasal Oxytocin Studies. *Biol. Psychiatry.* 79, 251-257.
- Wessman, J., Paunio, T., Tuulio-Henriksson, A., Koivisto, M., Partonen, T., Suvisaari, J., Turunen, J.A., Wedenoja, J., Hennah, W., Pietiläinen, O.P.H., Lönngqvist, J., Mannila, H., Peltonen, L., 2009. Mixture

Model Clustering of Phenotype Features Reveals Evidence for Association of DTNBP1 to a Specific Subtype of Schizophrenia. *Biol. Psychiatry*. 66, 990-996.

Zhang, Z., Xu, X., Ni, H., 2013. Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. *Crit. Care*. 17, R2.

Zheng, J., Babygirija, R., Bulbul, M., Cerjak, D., Ludwig, K., Takahashi, T., 2010. Hypothalamic oxytocin mediates adaptation mechanism against chronic stress in rats. *Am. J. Physiol. Gastrointest. Liver. Physiol*. 299, G946-953.

Zik, J.B., Roberts, D.L., 2015. The many faces of oxytocin: Implications for psychiatry. *Psychiatry. Res*. 226, 31-37.

Ms. Jenni Leppanen

PhD student

King's College London, Institute of Psychiatry, Psychology, and Neuroscience, Department of Psychological Medicine, London, United Kingdom

Dr. Kah Wee Ng

Psychiatrist

Singapore General Hospital, 20 College Road, Academia, Singapore, 169865

Dr. Youl-Ri Kim

Psychiatrist

Department of Psychiatry, Seoul Paik Hospital, Inje University, Seoul, South Korea

Dr. Kate Tchanturia

Reader in Psychology

Clinical Psychologist

King's College London, Institute of Psychiatry, Psychology, and Neuroscience, Department of Psychological Medicine, London, United Kingdom

Prof. Janet Treasure

Consultant Psychiatrist

Professor of Psychiatry

King's College London, Institute of Psychiatry, Psychology, and Neuroscience, Department of Psychological Medicine, London, United Kingdom

9 Figure legends

Figure 1. Literature search flow diagram

Figure 2. Forest plot of studies investigating the effects of intranasal oxytocin on physiological response to threat. Grillon et al. 2013(a) = female participants, Grillon et al. 2013(b) = male participants, Angry faces (f) = angry female faces, Angry faces (m) = angry male faces, EMG = electromyography.

Figure 3. Forest plot of studies investigating the effects of intranasal oxytocin on attentional bias towards social threat. Ellenbogen et al. 2012 (a) = congruent trials, Ellenbogen et al. 2012 (b) = incongruent trials, AN = anorexia nervosa; BN = bulimia nervosa; BPD = borderline personality disorder, ms = milliseconds.

Figure 4. Forest plot of studies investigating the effects of intranasal oxytocin on attentional bias towards disorder specific threat. Leppanen et al 2017 (a) = before smoothie challenge, Leppanen et al 2017 (b) = after smoothie challenge, AN = anorexia nervosa, BN = bulimia nervosa, ms = milliseconds, ITI = inter-trial interval.

Figure 5. Forest plot of studies investigating the effects of intranasal oxytocin on fixation towards regions of interest in threatening images. Lischke et al. 2012a used predefined regions of interest based on pilot data. ROI = region of interest, BPD = borderline personality disorder.

Table 1. Study characteristics

Study	Design	Dose (IU)	Dose-to-task interval	Group N	Age Mean (SD)	Task	Measure	Stimuli	ES [95 % CI]	Power (80 %)
Healthy										
Acheson et al. 2013	Between subjects	24 IU	45 min	Healthy Oxytocin = 22 Placebo = 22 % female = 47.75	Oxytocin = 28.2 (6.0) Placebo = 35.5 (21.1)	Fear conditioning (late acquisition)	EMG startle magnitude	Conditioned stimulus	0.03 [-0.57, 0.62]	No
Bertsch et al. 2013	Between subjects	24 IU	45 min	Healthy Oxytocin = 21 Placebo = 20 % female = 100	Oxytocin = 24.6 (3.9) Placebo = 24.4 (4.4)	Fixation during emotion recognition task	Fixation changes	Eyes of angry faces	-0.12 [-0.74, 0.49]	No
								Mouth of angry faces	0.31 [-0.31, 0.92]	
Brune et al. 2013	Within subjects (sessions 5-7 days apart)	24 IU	45 min	Healthy N = 13 % female = 76.92	25.7 (6.76)	Dot-probe (200ms/500ms stimulus presentation with 500ms ITI)	Attentional bias	Angry faces	-1.64 [-2.47, -0.81]	No
Clark-Elford et al. 2015	Within subjects (sessions 7 days apart)	24 IU	45 min	Healthy N = 26 % female = 0	26.00 (6.32)	Dot-probe (500ms stimulus presentation with 500-1250ms ITI)	Attentional bias	Angry faces	0.04 [-0.35, 0.42]	No
Domes et al. 2013	Between subjects	24 IU	40 min	Healthy Oxytocin = 30 Placebo = 32 % female = 0	Oxytocin = 23.9 (0.4) Placebo = 24.4 (0.5)	Fixation during emotion recognition task	Relative fixation duration	Eyes of angry faces	0.28 [-0.78, 0.22]	No

Eckstein et al. 2015	Between subjects	24 IU	30 min	Healthy Oxytocin = 18 Placebo = 18 % female = 0	Oxytocin = 25.20 (4.46) Placebo = 24.03 (4.08)	Fear conditioning (late acquisition)	Skin conductance startle response	Conditioned stimulus	0.50 [-0.15, 1.16]	No
Eckstein et al. 2016	Between subjects	24 IU	30 min	Healthy Oxytocin = 17 Placebo = 30 % female = 0	Oxytocin = 24.17 (3.58) Placebo = 24.61 (4.28)	Fear conditioning (late acquisition)	Skin conductance startle response	Conditioned stimulus	0.72 [0.10, 1.33]	No
Ellenbogen et al. 2012	Between subjects	24 IU	45 min	Healthy Oxytocin = 29 Placebo = 28 % female = 52.63	Oxytocin = 23.2 (3.3) Placebo = 23.6 (3.5)	SCT: Engagement (masked stimulus presentation with 1850-2500ms ITI)	Attentional bias	Angry faces	0.10 [-0.42, 0.61]	No
						SCT: Engagement (200ms stimulus presentation with 1850-2500ms ITI)			0.00 [-0.51, 0.51]	
						SCT: Engagement (750ms stimulus presentation with 1850-2500ms ITI)			-0.12 [-0.64, 0.39]	
						SCT: Avoidance (masked stimulus presentation with 1850-2500ms ITI)			0.09 [-0.42, 0.61]	

						SCT: Avoidance (200ms stimulus presentation with 1850-2500ms ITI)			- 0.31 [- 0.83 , 0.21]	
						SCT: Avoidance (750ms stimulus presentation with 1850-2500ms ITI)			0.03 [- 0.48 , 0.55]	
Grillon et al. 2013	Within subjects (N of days between sessions NR)	24 IU	55 min	Healthy Male = 24	NR	Electric shock induced startle during cue presentation task	Eye blink startle response	Predictable shock	0.03 [- 0.37 , 0.43]	No
								Unpredictable shock	0.19 [- 0.21 , 0.60]	
								Predictable shock	- 0.03 [- 0.48 , 0.42]	
								Unpredictable shock	0.07 [- 0.38 , 0.52]	
Hubble et al. 2017	Within subjects (sessions 14 days apart)	24 IU	30min	Healthy N = 30 % female = 0	20.98 (4.55)	Fixation during emotion recognition task	Relative fixation duration	Eyes of angry faces	- 0.11 [- 0.47 , 0.24]	No
								Mouth of angry faces	- 0.23 [- 0.60 , 0.13]	

]	
								Eyes of disgust faces	0.005 [-0.35, 0.36]	
								Mouth of disgust faces	0.005 [-0.35, 0.36]	
Kim et al. 2014a	Within subjects (sessions 4-7 days apart)	40 IU	45 min	Healthy N = 33 % female = 100	22.18 (2.14)	Dot-probe (500ms stimulus presentation with 750ms ITI)	Attentional bias	Angry faces	-0.21 [-0.55, 0.14]	No
								Disgust faces	-0.53 [-0.90, -0.17]	
Kim et al. 2014b	Within subjects (sessions 7 days apart)	40 IU	45 min	Healthy N = 31 % female = 100	22.2 (2.2)	Dot-probe (1000ms stimulus presentation with 750ms ITI)	Attentional bias	Angry faces	-0.20 [-0.55, 0.16]	No
								Disgust faces	-0.47 [-0.84, -0.10]	
Leknes et al. 2013	Within subjects (N of days between sessions NR)	40 IU	40 min	Healthy N = 39 % female = 51.28	26 (range = 20-39)	Startle response during emotion evaluation task	Pupil dilation startle response	Angry faces	0.44 [0.11, 0.77]	Yes
Lischke et al. 2012a	Within subjects	24 IU	45 min	Healthy N = 14 % female =	23.79 (2.32)	Fixation during passive viewing	Fixation duration	Predefined ROI in negative scenes	0.00 [-0.52,]	No

	(sessions 4 weeks apart)			100		of scenes			0.52]	
							Fixation counts		0.37 [- 0.17 , 0.91]	
Lischke et al. 2012b	Between subjects	24 IU	45 min	Healthy Oxytocin = 20 Placebo = 24 % female = 0	Total: 26.09 (3.41)	Fixation during emotion recognition	Relative fixation duration	Eyes of angry faces	0.38 [- 0.22 , 0.97]	No
								Mouth of angry faces	- 0.45 [- 1.04 , 0.15]	
Preckel et al. 2014	Between subjects	24 IU	45 min	Healthy Oxytocin = 33 Placebo = 34 % female = 100	Oxytocin = 23.61 (2.71) Placebo = 23.74 (2.47)	Approach / avoidance task	Approach reaction time (ms)	Negative social stimuli	0.34 [- 0.14 , 0.83]	No
								Negative non-social stimuli	- 0.07 [- 0.55 , 0.41]	
Prehn et al. 2013	Between subjects	24 IU	45 min	Healthy Oxytocin = 23 Placebo = 24 % female =	Oxytocin = 25.78 (3.37) Placebo = 26.38 (3.49)	Startle response during emotion recognition task	Pupil dilation startle response	Angry male faces	0.54 [- 0.04 , 1.12]	No
								Angry female faces	0.26 [- 0.31 , 0.84]	
Radke et al. 2013	Within subjects (sessions 14 days apart)	24 IU	45 min	Healthy N = 24 % female = 0	21.46 (1.93)	Approach / avoidance task	Approach / avoidance bias	Angry faces	0.52 [0.09, 0.95]	No

)									
Radke et al. 2017	Between subjects	24 IU	45 min	Healthy Oxytocin = 24 Placebo = 28 % female = 0	Total: 22.4 (3)	Approach / avoidance task	Approach reaction time (ms)	Angry faces	- 0.51 [- 1.07, 0.04]	No
							Avoidance reaction time (ms)		- 0.56 [- 1.11, - 0.002]	
Striepen et al. 2012	Between subjects	24 IU	45 min	Healthy Oxytocin = 36 Placebo = 33 % female = 0	Oxytocin = 24.28 (2.86) Placebo = 25.03 (2.56)	Startle response to negative images	Eye blink magnitude startle response	Negative IAPS images	0.70 [0.21, 1.18]	
Theodoridou et al. 2013	Between subjects	24 IU	35 min	Healthy Oxytocin = 60 Placebo = 60 % female = 50	Total: 22.4 (range = 18.1-43.8)	Approach / avoidance task	Approach reaction time (ms)	Angry faces	NR*	No
							Avoidance reaction time (ms)	Disgusted faces		
								Angry faces		
								Disgusted faces		
Clinical										
Bertsch et al. 2013	Between subjects	24 IU	45 min	BPD Oxytocin = 19 Placebo = 19 % female = 100	Oxytocin = 23.2 (5.3) Placebo = 24.9 (5.5)	Fixation during emotion recognition task	Fixation changes	Eyes of angry faces	- 0.70 [- 1.33, - 0.06]	No
								Mouth of angry faces	- 0.21 [- 0.85, 0.44]	
Brune et al. 2013	Within subjects (sessions 5-7 days)	24 IU	45 min	BPD N = 13 % female = 61.54		Dot-probe (200ms/500ms stimulus presentation with 500ms)	Attentional bias	Angry faces	1.30 [0.56, 2.04]	No

	apart)					ITI)				
Clark-Elford et al. 2015	Within subjects (sessions 7 days apart)	24 IU	45 min	Highly anxious people N = 16 % female = 0	27.13 (9.25)	Dot-probe (500ms stimulus presentation with 500-1250ms ITI)	Attentional bias	Angry faces	- 0.42 [- 0.93 , 0.09]	No
Domes et al. 2016	Between subjects	24 IU	60 min	Depression Oxytocin = 22 Placebo = 21 % female = 58.14	Oxytocin = 46.7 (11.1) Placebo = 47.2 (9.0)	Dot-probe (100ms stimulus presentation with 750-1500ms ITI)	Attentional bias	Angry faces	0.50 [- 0.10 , 1.10]	No
						Dot-probe (600ms stimulus presentation with 750-1500ms ITI)			0.14 [- 0.46 , 0.73]	
						Dot-probe (1200ms stimulus presentation with 750-1500ms ITI)			- 0.33 [- 0.93 , 0.27]	
Kim et al. 2014a	Within subjects (sessions 4-7 days apart)	40 IU	45 min	AN N = 31 % female = 100	23.10 (9.35)	Dot-probe (500ms stimulus presentation with 750ms ITI)	Attentional bias	Angry faces	0.50 [0.13, 0.87]	No
								Disgusted faces	- 0.28 [- 0.64 , 0.08]	
Kim et al. 2014c	Within subjects (sessions)	40 IU	45 min	AN N = 31 % female = 100	23.10 (9.35)	Dot-probe (1000ms stimulus presentation with	Attentional bias	Food-related stimuli	- 0.40 [- 0.77 , - 0.03]	No

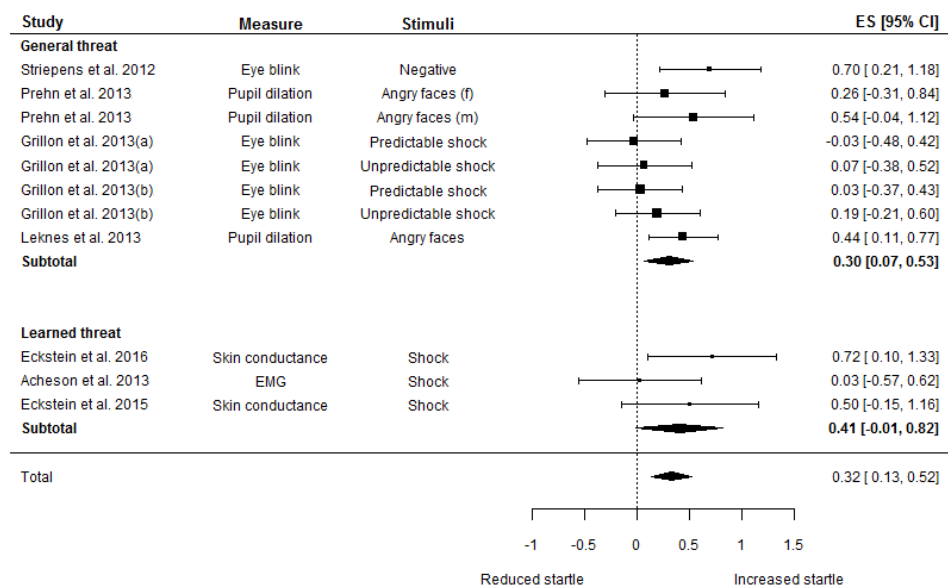
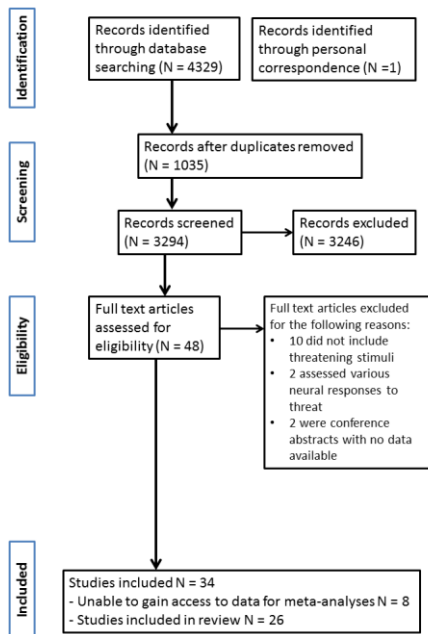
	4-7 days apart)					750ms ITI)]	
								Body shape-related stimuli	- 0.38 [- 0.75 , - 0.02]	
								Body weight-related stimuli	0.02 [- 0.33 , 0.37]	
Kim et al. In prep.	Within subjects (sessions)	40 IU	45 min	BN N = 31 % female = 100	23.87(3.99)	Dot-probe (500ms stimulus presentation with 750ms ITI)	Attentional bias	Angry faces	- 0.22 [- 0.57 , 0.14]	No
								Disgusted faces	0.09 [- 0.26 , 0.44]	
								Food-related stimuli	0.12 [- 0.23 , 0.47]	
								Body shape-related stimuli	0.36 [- 0.00 02, 0.73]	
								Body weight-related stimuli	- 0.00 5 [- 0.36 , 0.35]	
						Dot-probe (1000ms stimulus presentation with 750ms ITI)		Angry faces	- 0.47 [- 0.84 , - 0.10]	
								Disgusted faces	0.04 [-	

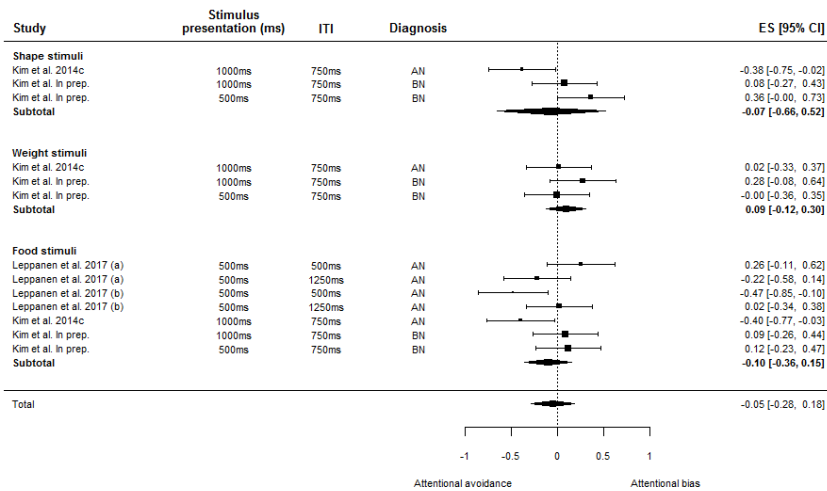
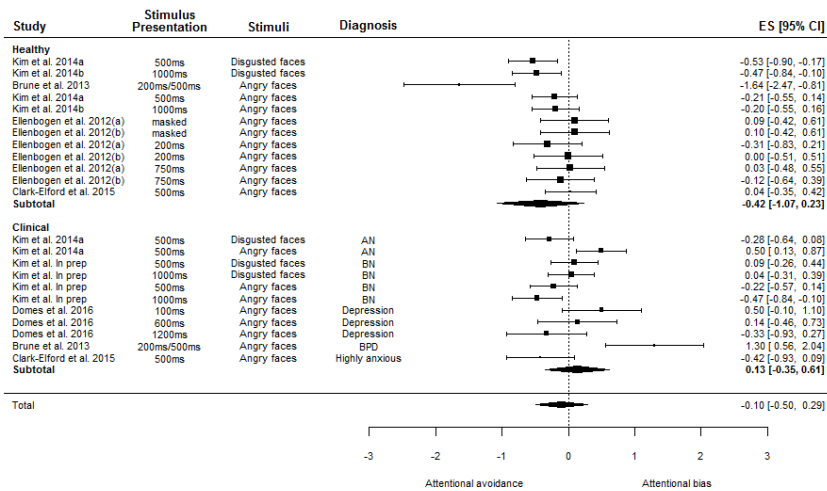
									0.31 [0.39]	
								Food- related stimuli	0.09 [0.26 , 0.44]	
								Body shape- related stimuli	0.08 [0.27 , 0.43]	
								Body weight- related stimuli	0.28 [0.08 , 0.64]	
Leppanen et al. 2017	Withi n subje cts (sessi ons 1-5 days apart)	40 IU	55 min (befor e smoot hie challe nge)	AN N = 30 % female = 100	26.2 (6.82)	Dot- probe (500ms stimulus presentat ion with 500ms ITI)	Attentio nal bias	Food- related stimuli	0.26 [0.11 , 0.62]	No
						Dot- probe (500ms stimulus presentat ion with 1250ms ITI)			- 0.22 [0.58 , 0.14]	
			80 min (after smoot hie challe nge)			Dot- probe (500ms stimulus presentat ion with 500ms ITI)			- 0.47 [0.85 , - 0.10]	
						Dot- probe (500ms stimulus presentat ion with 1250ms ITI)			0.02 [0.34 , 0.38]	
Mitchell et al. 2016	Withi n	40 IU	30 min	Alcohol depend	28.9 (7.15)	Approach /	Approach /	Negative IAPS	0.16 [-	No

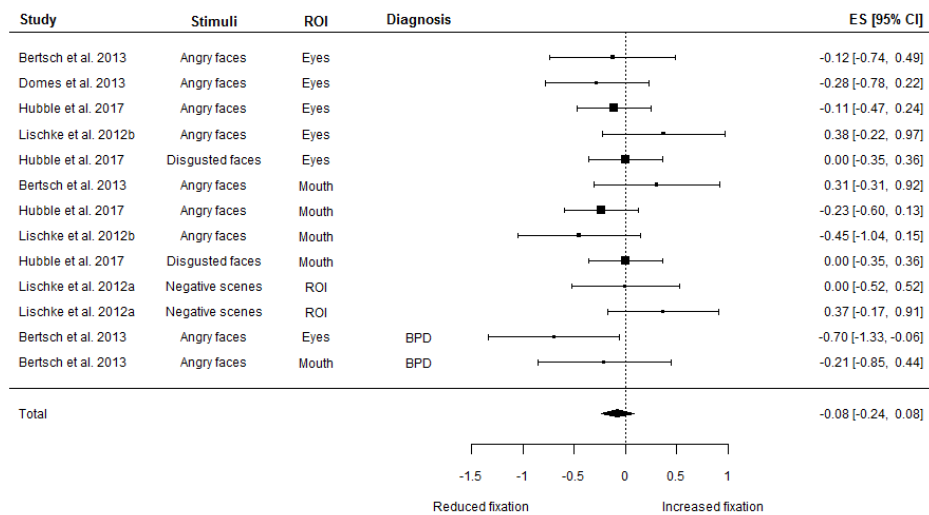
	subjects (sessions 7 days apart)			borderline Disorder N = 32 % female = 40.63		avoidance task	avoidance bias	images	0.19 , 0.51]	
--	---	--	--	--	--	-------------------	-------------------	--------	------------------------	--

ES = effect size estimate (either standardised mean difference or standardised mean change); IU = international unit; SD = standard deviation; EMG = electromyography; min = minutes; ms = milliseconds; ES = effect size; SCT = spatial cueing task; ITI = inter-trial interval; ROI = region of interest; IAPS = International Affective Picture System; BPD = borderline personality disorder; AN = anorexia nervosa; BN = bulimia nervosa; NR = not reported. The Power column indicates whether or not the studies met our sample size requirement to have 80% power to detect at least a moderate difference between oxytocin and placebo.

*Relevant data was not reported in the paper







Highlights

- The review explores the effects of intranasal oxytocin on threat processing
- Intranasal oxytocin increased startle response to threat in healthy people
- No significant effects on attentional or approach responses were observed